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## Prognostic risk factor analysis and construction of a nomogram for elderly primary liver cancer patients based on SEER database

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4 **Prognostic risk factor analysis and construction of a nomogram for elderly**  
5 **primary liver cancer patients based on SEER database**  
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43 **Running title:** Nomogram model for primary liver cancer in elderly patients  
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46 **Key words:** nomogram, primary liver cancer, elderly, database  
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## Abstract

**Objective:** To evaluate the risk factors and construct a nomogram model for the prognosis of primary liver cancer in the elderly based on the data from the US SEER database. **Methods:** The latest data of primary liver cancer patients were extracted from the SEER database with SEER\*STAT software, and the required variables were included. The data was screened and then divided into training cohort and validation cohort. Variates were first screened by univariate and multivariate COX analysis, and variates with then statistical significance were included the construction of a nomogram model. The C-Index, ROC and calibration curves were used to evaluate the model. **Results:** A total of 10824 eligible cases from 2004 to 2017 were extracted, among which, 7757 cases were included in the training cohort and 3247 in the validation cohort. The C-Index of the model was 0.747 (training cohort) and 0.773 (validation cohort). The 3-year AUCs of the training and validation cohort were 0.760 and 0.750, while the 5-year AUCs were 0.761 and 0.748. The calibration curves showed an ideal calibration of the constructed model. **Conclusions:** The nomogram model constructed followed by COX regression analysis showed ideal calibration and discrimination property, and can provide a reference for clinical application of elderly primary liver cancer in the future.

### Strength and limitations of this study:

#### Strength:

1. Collected a large and sufficient number of cases from SEER database of elderly liver cancer.
2. Constructed a novel and ideal prognostic model for elderly liver cancer

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#### Limitations:

- 1.All cases were collected form one database and selection bias might exist.
- 2.Some classification carried out by SEER database was not very specific.
- 3.Information such as ancillary tests was absent from the SEER database.

**Keywords:** nomogram, primary liver cancer, elderly, database

#### Introduction

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Primary liver cancer is currently the sixth most common cancer worldwide and, according to epidemiological surveys, is the fourth leading cause of cancer-related deaths globally, representing a major threat to the health of the entire human population <sup>[1,2]</sup>. Furthermore, many studies have pointed out that although middle-aged (30-59 years old) or young (< 30 years old) patients with primary liver cancer are not uncommon worldwide, the average age of diagnosis of the disease is 60 years old and, in contrast to the yearly decrease in the age-standardized incidence rate (ASR) of young patients, the incidence of elderly patients has continuously increased in more than half of

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4 the countries and regions during the last 30 years [3-5]. The global population expansion, increasing  
5 aging, as well as obesity, diabetes, overmedication and lagging effects of HBV infection in the  
6 elderly may be responsible for the high or even increasing ASR of primary liver cancer in elderly  
7 patients, creating a heavy burden on the health of all countries [6-8]. In terms of treatment, surgery  
8 remains the first choice for primary liver cancer. Therefore, based on the epidemiological  
9 characteristics and treatment modalities of the disease, it is necessary to conduct an accurate  
10 prognostic assessment of elderly patients with primary liver cancer to guide clinical work.  
11 However, the different pathological types and heterogeneity of the disease make prognostic  
12 assessment still difficult.  
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22 Recently, the nomogram model has shown superior predictive performance over the  
23 traditional TNM staging because of its convenient modeling method and the ability to incorporate  
24 multiple variables, thus gaining widespread popularity [9,10]. This study intended to use a  
25 nomogram model to analyze the risk factors affecting elderly primary liver cancer in the SEER  
26 database and to predict the prognosis of the disease. The assessment performance of the model  
27 was analyzed by the test of discrimination and calibration to establish an optimal assessment  
28 system for clinical work such as the treatment of elderly primary liver cancer.  
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## 39 **Methods and data**

### 40 41 42 43 44 1. Ethical statement

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46 Informed consent was not required from patients to obtain data from the US SEER database  
47 since cancer is publicly reportable in every state in the United States.  
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### 50 51 2. Case selection

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53 Case data of primary liver cancer with complete follow-up records were selected from the  
54 2004-2017 SEER database (SEER research data, 18 Registries, Nov 2019 Sub (2000-2017)) using  
55 SEER\*Stat 8.3.6. The extracted variables included race, year of diagnosis, age, sex, primary site,  
56 histologic type, grade, TNM stage, tumor size, surgery on the primary site, survival time, cause of  
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3 death and survival status. Among them, patients who were older than 65 years old were selected;  
4 Asian and Pacific Islanders, American Indians and Alaskan natives were included in Asian and  
5 others for the race variable; liver or intrahepatic bile duct (IBD) was selected as the primary site;  
6 intrahepatic cholangiocarcinoma (ICC), hepatocellular carcinoma (HCC), and combined hepatic  
7 carcinoma (CHC) were selected as the histologic type; and local destruction included  
8 photodynamic therapy (PDT), percutaneous ethanol injection (PEI) and radiofrequency ablation  
9 (RFA), etc.

### 17 3. Statistical processing

20 The optimal cut-off value of tumor size was analyzed using the X-Tile software, and the  
21 variable was classified into < 46 mm, 46-81 mm and > 81 mm according to high, medium and low  
22 risk. After that, the total cases were randomly assigned to a training or a validation cohort at a  
23 ratio of 7:3 using SPSS 18.0 by random number 20200222, followed by the collection of baseline  
24 information. Univariate and multivariate (Forward: LR) COX analyses were performed using the  
25 R software or SPSS to screen for statistically significant variables to construct a nomogram, based  
26 on which C-Index, ROC curves and the area under the curve (AUC) were figured out. Calibration  
27 curves of the model for 3 and 5 years were plotted with the R software after Bootstrap sampling  
28 for 1000 times.  $P < 0.05$  was considered statistically significant.

## 41 Results

### 47 1. Clinical characteristics of the cases

49 A total of 10,824 elderly cases with primary liver cancer were extracted in accordance with  
50 screening conditions, with 7,757 included in the training cohort and 3,247 in the validation one.  
51 Among them, the majority of patients were male (67.5%), white (71.3%), with primary site in the  
52 liver (87.8%), HCC (84.7%), grade II (46.6%), T1 (46.5%), N0 (91.6%), M0 (88.7%) and  
53 unoperated (56.5%) (Table 1).



## 2. Screening for prognostic risk factors

Univariate COX regression analysis of the training cohort proved the variates of age, sex, race, histological type, grade, TNM stage, surgery and tumor size to be statistically significant ( $P < 0.05$ ), which were included in the follow-up multivariate COX analysis. However, the primary site was excluded according to the analysis ( $P = 0.232$ ) (Table 2). Subsequently, the sex variable was further excluded from the experiment by Forward: LR multivariate COX (Table 3). In conclusion, age, race, histological type, grade, TNM stage, surgery, and tumor size were independent risk factors that affect the prognosis of elderly patients from the extracted data with primary liver cancer, which could be used to construct a subsequent nomogram prediction model.

## 4. Nomogram model construction and verification

The independent risk factors affecting prognosis derived from the above analysis were incorporated to construct a 3- and 5-year nomogram prediction model for elderly primary liver cancer, and the total score was calculated by aggregating the scores of each variable to predict the survival rate of patients at 3 and 5 years (Figure 1). It can be seen that the surgery on the primary site was the most important factor affecting the score in this model, followed by tumor size, TNM stage and age. The AUC was calculated after plotting the ROC curves of the training and validation cohorts. Specifically, the AUC is 0.760 (3 years) and 0.761 (5 years) in the training cohort and 0.750 (3 years) and 0.748 (5 years) in the validation cohort (Figure 2). Furthermore, the model showed an ideal calibration for 3 and 5 years in both groups after creating the calibration curves for the training and validation cohorts (Figure 3).

## Discussion

Analysis of cases revealed that male patients accounted for more than 60% of elderly patients

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4 with primary liver cancer. Some statistics have presented that the mean annual change rate of men  
5 suffering from the disease is higher than that of women (3.7% vs. 2.7%) in the United States [11].  
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7 In China, a population-based study of hepatic carcinoma in Zhejiang Province demonstrated that  
8 the ASR for hepatic carcinoma was 33.24 in men compared to 1.21 in women [12]. Not only  
9 differences in lifestyle---including alcohol consumption and smoking---have led to higher cancer  
10 rates in men, but different physiological conditions such as hormone secretion and even genetic  
11 differences may be responsible for these epidemiological differences [13]. Therefore, it has been  
12 put forward that gender is a critical biological variable that should be considered in all studies  
13 aimed at improving carcinoma [14]. Analysis of baseline data also suggested that the population of  
14 elderly primary liver cancer was predominantly white and mostly with the primary site in the liver,  
15 HCC histological type, grade II (moderately differentiated), T1 and without lymph node  
16 metastasis or distant metastasis. Moreover, in this population, more than half of the cases were not  
17 treated surgically. The reason for this phenomenon may be that most of the patients were over 60  
18 years old at the time of diagnosis, missing the best timing for radical surgery, together with the  
19 decline in physical function as well as intolerance to surgery led to a palliative treatment for most  
20 patients.  
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35 Based on further univariate and multivariate COX analyses, several independent risk factors  
36 that affect the prognosis of the disease were sifted out, including age, race, histological type,  
37 grade, TNM stage, surgery and tumor size. Sex, though not negligible as previously mentioned,  
38 was found not to be the main factor affecting prognosis in this population after comprehensive  
39 analysis, which is consistent with several current retrospective studies on hepatic carcinoma  
40 [15-17]. In terms of histological type, it is evident that CHC has a worse prognosis than the  
41 common HCC, which shows a lower incidence but a higher malignancy [18-19]. Analysis of the  
42 age factor revealed that the higher the age group of the patient, the worse the prognosis,  
43 suggesting a linear negative correlation trend. The nomogram model also indicated that the  
44 surgery option was the most crucial factor influencing the prognosis of the disease. The patients  
45 who underwent liver transplantation, though small in number, showed a relatively good  
46 prognosis, followed by resection or lobectomy and then by local destruction. In contrast, patients  
47 without surgery showed a poor prognosis. This factor alone reduced the 3- and 5-year predicted  
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4 survival rates to less than 50%, suggesting that the invention of new methods or enhanced  
5 surgery is still an urgent issue for improving the prognosis of elderly primary liver cancer. The  
6 influence of other factors on prognosis is basically in line with the current consensus that the  
7 worse the grade, the higher the T-stage, the occurrence of lymph node metastasis, the occurrence  
8 of distant metastasis and the larger the tumor, the worse the prognosis of the patient.  
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14 After that, the performance of the established model was evaluated by C-Index, ROC  
15 curves and calibration curves. A nomogram model is considered to have good discrimination if  
16 its C-Index and AUC exceed 0.7 [20,21]. As the model constructed in this study had these two  
17 indicators above 0.7 in both the training and validation cohorts and the calibration plots scatter in  
18 accordance with the reference line, it could be considered that the model has good discrimination  
19 and calibration and hence the capacity to predict the prognosis of the disease.  
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26 However, this study also has shortcomings. First, the cases were all from the US SEER  
27 database, which is not representative of regions other than the United States and is subject to  
28 selection bias. In addition, the case data included in this database lacked some important  
29 ancillary tests related to the diagnosis and treatment of liver cancer, such as CEA, AST and  
30 vascular invasion.  
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37 In conclusion, a nomogram model with favorable prediction was developed by using the  
38 case data from the SEER database after performing univariate and multivariate COX screening,  
39 which could provide a reference for the future diagnosis and treatment of elderly patients with  
40 primary liver cancer.  
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#### 58 **Conflicts of interest**

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3 The authors declare there are no competing interests.  
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### 8 **Author contributions**

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11 Fangyuan Li wrote and revised the manuscript; Ting Zheng conducted most of the analysis of  
12 data; Xuewei Gu reviewed the manuscript; All authors read and approved the final manuscript.  
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### 16 **Availability of data and material**

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19 The datasets used and/or analyzed during the current study are available from the corresponding  
20 author on reasonable request.  
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### 26 **Patient and Public Involvement**

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29 No patient involved.  
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### 36 **Ethics approval and consent to participate**

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39 Informed consent was not required from patients to obtain data from the US SEER database since  
40 cancer is publicly reportable in every state in the United States.  
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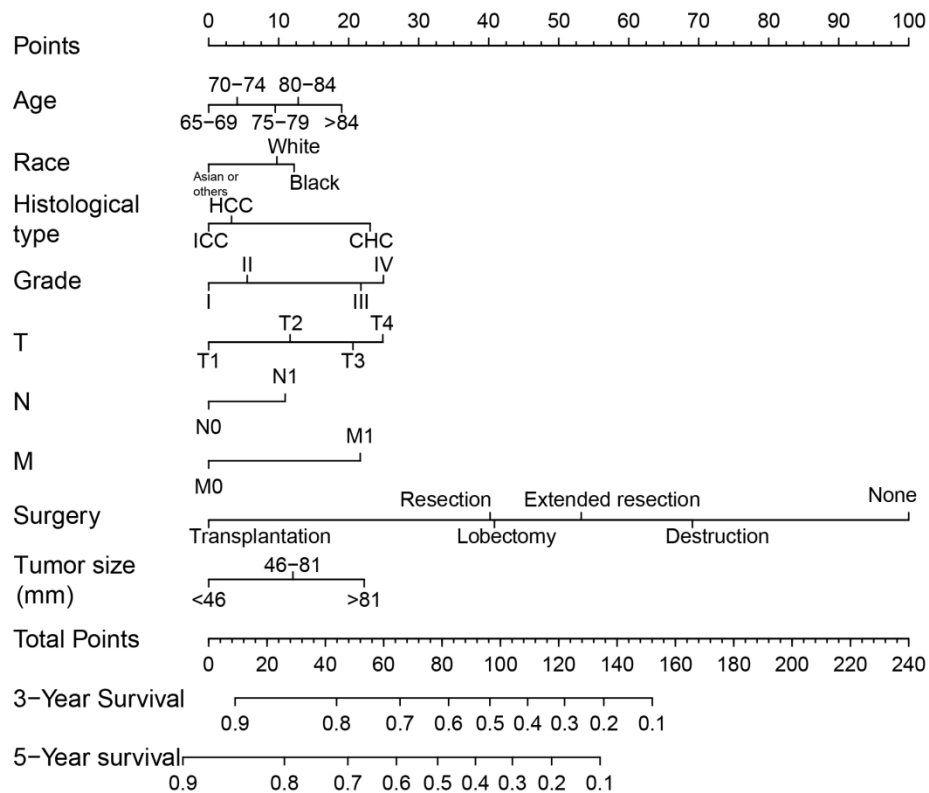
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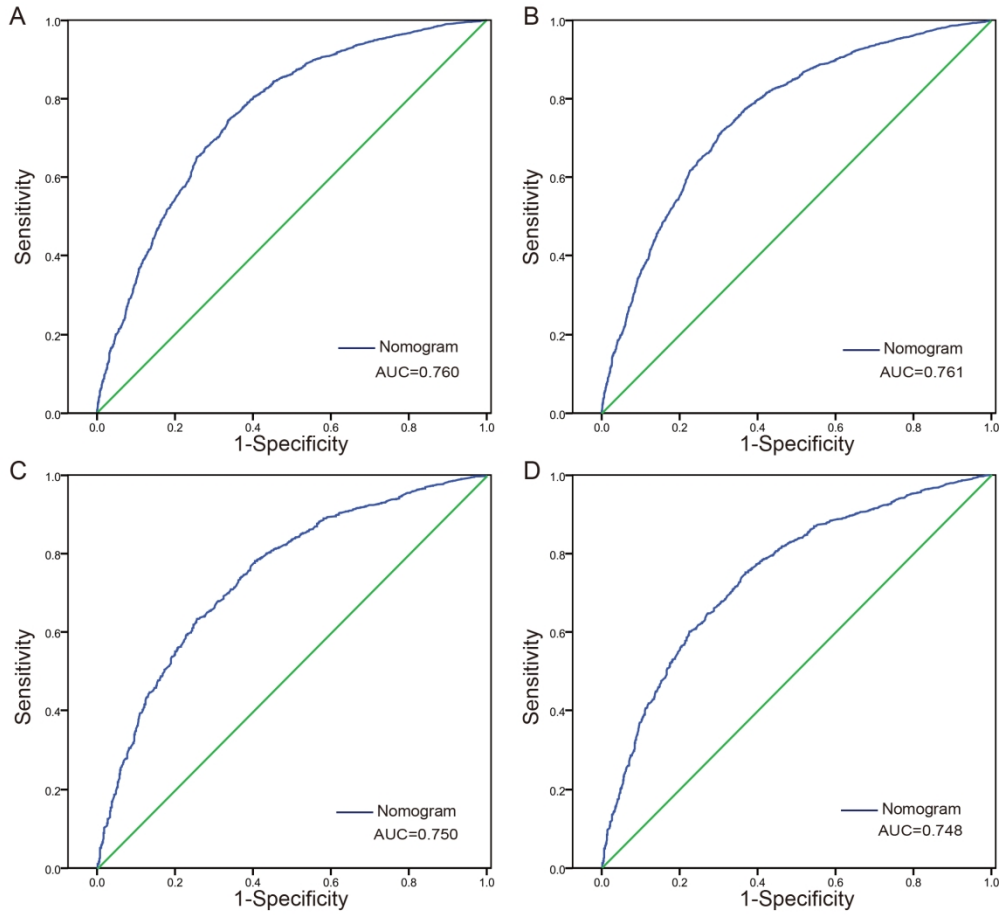
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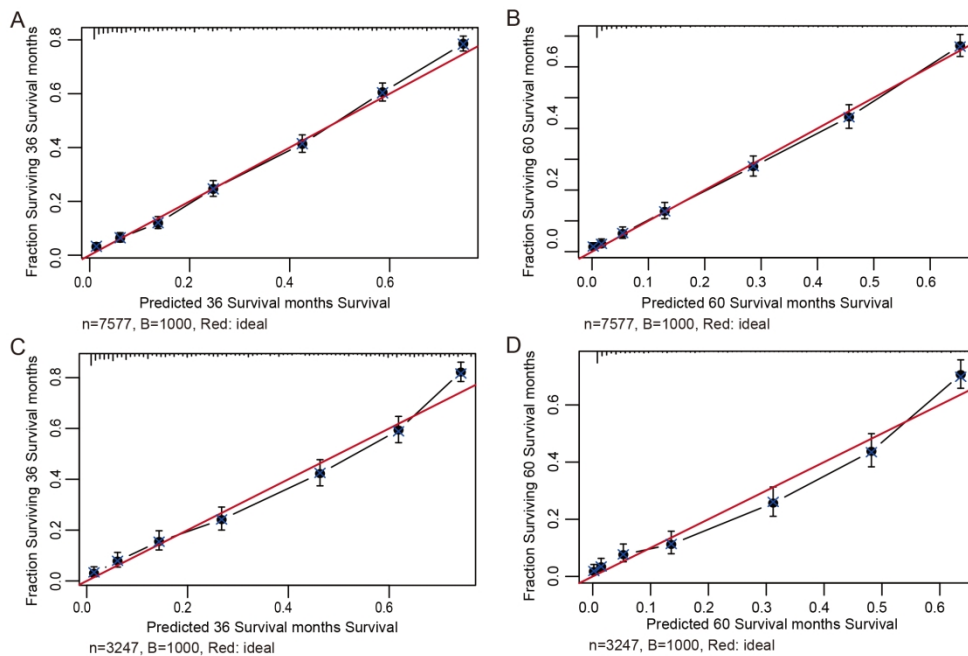
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**Table 1** Baseline data of extracted cases

Variates	Total cohort 10824(100%)	Training cohort 7577(100%)	Validation cohort 3247(100%)
<b>Age</b>			
65-69	3600(33.3%)	2540(33.5%)	1060(32.6%)
70-74	2829(26.1%)	1994(26.3%)	835(25.7%)
75-79	2228(20.6%)	1544(20.4%)	684(21.1%)
80-84	1451(13.4%)	1001(13.2%)	450(13.9%)
>84	716(6.61%)	498(6.57%)	218(6.71%)
<b>Sex</b>			
Male	7309(67.5%)	5122(67.6%)	2187(67.4%)
Female	3515(32.5%)	2455(32.4%)	1060(32.6%)
<b>Race</b>			
White	7722(71.3%)	5390(71.1%)	2332(71.8%)
Black	956(8.83%)	672(8.87%)	284(8.75%)
Asian or others	2146(19.8%)	1515(20.0%)	631(19.4%)
<b>Primary site</b>			
Liver	9508(87.8%)	6674(88.1%)	2834(87.3%)
IBD	1316(12.2%)	903(11.9%)	413(12.7%)
<b>Histological type</b>			
HCC	9171(84.7%)	6419(84.7%)	2752(84.8%)
ICC	1570(14.5%)	1095(14.5%)	475(14.6%)
CHC	83(0.77%)	63(0.83%)	20(0.62%)
<b>Grade</b>			
I	3108(28.7%)	2163(28.5%)	945(29.1%)
II	5040(46.6%)	3510(46.3%)	1530(47.1%)
III	2504(23.1%)	1785(23.6%)	719(22.1%)
IV	172(1.59%)	119(1.57%)	53(1.63%)
<b>T</b>			
T1	5028(46.5%)	3523(46.5%)	1505(46.4%)
T2	2547(23.5%)	1786(23.6%)	761(23.4%)
T3	2765(25.5%)	1932(25.5%)	833(25.7%)
T4	484(4.47%)	336(4.43%)	148(4.56%)
<b>N</b>			
N0	9910(91.6%)	6931(91.5%)	2979(91.7%)
N1	914(8.44%)	646(8.53%)	268(8.25%)
<b>M</b>			
M0	9605(88.7%)	6716(88.6%)	2889(89.0%)
M1	1219(11.3%)	861(11.4%)	358(11.0%)
<b>Surgery</b>			
Resection	1901(17.5%)	1315(17.4%)	586(18.0%)
Lobectomy	1116(10.3%)	807(10.7%)	309(9.52%)

Transplantation	328(3.03%)	238(3.14%)	90(2.77%)
Destruction	1087(10.0%)	769(10.1%)	318(9.79%)
Extended resection	277(2.56%)	195(2.56%)	82(2.53%)
None	6115(56.5%)	4253(56.1%)	1862(57.3%)
<b>Tumor size(mm):</b>			
<46	4168(38.5%)	2925(38.6%)	1243(38.3%)
46-81	3532(32.6%)	2491(32.9%)	1041(32.1%)
>81	3124(28.9%)	2161(28.5%)	963(29.7%)

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**Table 2** Univariate COX analysis

Variates	P-value	Hazard ratio	95%CI lower	95%CI upper
<b>Age</b>	<b>&lt;0.001</b>			
65-69	Reference			
70-74	<0.001	1.168	1.085	1.257
75-79	<0.001	1.420	1.314	1.534
80-84	<0.001	1.639	1.502	1.788
>84	<0.001	2.072	1.855	2.314
<b>Sex</b>	<b>0.003</b>			
Male	Reference			
Female	0.003	0.914	0.862	0.969
<b>Race</b>	<b>&lt;0.001</b>			
White	Reference			
Black	0.224	1.062	0.964	1.170
Asian or others	<0.001	0.737	0.685	0.792
<b>Primary site</b>	<b>0.232 (Excluded)</b>			
Liver	Reference			
IBD	0.232	1.055	0.967	1.151
<b>Histological type</b>	<b>0.032</b>			
HCC	Reference			
ICC	0.383	0.881	0.663	1.171
CHC	0.861	0.974	0.727	1.305
<b>Grade</b>	<b>&lt;0.001</b>			
I	Reference			
II	0.043	0.934	0.875	0.998
III	<0.001	1.464	1.360	1.577
IV	0.001	1.437	1.162	1.776
<b>T</b>	<b>&lt;0.001</b>			
T1	Reference			
T2	<0.001	1.213	1.129	1.304
T3	<0.001	2.446	2.290	2.614
T4	<0.001	2.493	2.200	2.825
<b>N</b>	<b>&lt;0.001</b>			
N0	Reference			
N1	<0.001	2.265	2.072	2.476
<b>M</b>	<b>&lt;0.001</b>			
M0	Reference			
M1	<0.001	3.025	2.798	3.271
<b>Surgery</b>	<b>&lt;0.001</b>			
Resection	Reference			
Lobectomy	<0.001	0.234	0.213	0.256

Transplantation	<0.001	0.268	0.241	0.299
Destruction	<0.001	0.079	0.060	0.104
Extended resection	<0.001	0.366	0.332	0.403
None	<0.001	0.372	0.308	0.449
<b>Tumor size(mm):</b>	<b>&lt;0.001</b>			
<46	Reference			
46-81	<0.001	1.744	1.630	1.867
>81	<0.001	2.577	2.405	2.761

CI: confidence interval.

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**Table 3** Multivariates COX analysis

Variates	P-value	Hazard ratio	95%CI lower	95%CI upper
<b>Age</b>				
65-69	Reference			
70-74	0.029	1.086	1.009	1.170
75-79	<0.001	1.219	1.127	1.318
80-84	<0.001	1.307	1.196	1.428
>84	<0.001	1.484	1.326	1.660
<b>Sex</b>	<b>(Excluded)</b>			
Male				
Female				
<b>Race</b>				
White	Reference			
Black	0.325	1.051	0.952	1.159
Asian or others	<0.001	0.813	0.756	0.875
<b>Histological type</b>				
HCC	Reference			
ICC	0.159	0.940	0.863	1.024
CHC	0.005	1.508	1.132	2.010
<b>Grade</b>				
I	Reference			
II	0.001	1.121	1.047	1.199
III	<0.001	1.567	1.449	1.695
IV	<0.001	1.683	1.358	2.086
<b>T</b>				
T1	Reference			
T2	<0.001	1.282	1.190	1.381
T3	<0.001	1.542	1.435	1.657
T4	<0.001	1.689	1.484	1.923
<b>N</b>				
N0	Reference			
N1	<0.001	1.253	1.136	1.382
<b>M</b>				
M0	Reference			
M1	<0.001	1.556	1.429	1.694
<b>Surgery</b>				
Resection	Reference			
Lobectomy	0.833	1.014	0.889	1.157
Transplantation	<0.001	0.417	0.313	0.557
Destruction	<0.001	1.851	1.632	2.100
Extended resection	0.007	1.325	1.080	1.626

None	<0.001	3.552	3.229	3.906
<b>Tumor size(mm):</b>				
<46	Reference			
46-81	<0.001	1.291	1.199	1.391
>81	<0.001	1.597	1.474	1.730

CI: confidence interval.

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4 **Figure 1** Constructed nomogram  
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6 **Figure 2** 3- and 5-year survival ROC curves for the training and validation cohorts. A: 3-year  
7 survival ROC curve for the training cohort. B: 5-year survival ROC curve for the training cohort.  
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9 C: 3-year survival ROC curve for the validation cohort. D: 5-year survival ROC curve for the  
10 validation cohort.  
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15 **Figure 3** 3- and 5-year survival calibration curves for the training and validation cohorts. A:  
16 3-year survival calibration curve for the training cohort. B: 5-year survival calibration curve for  
17 the training cohort. C: 3-year survival calibration curve for the validation cohort. D: 5-year  
18 survival calibration curve for the validation cohort.  
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**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology\***  
**Checklist for cohort, case-control, and cross-sectional studies (combined)**

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	5

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Prognostic risk factor analysis and construction of a nomogram for elderly primary liver cancer patients based on SEER database

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<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	Cancer genetics < GENETICS, Adult oncology < ONCOLOGY, Gene therapy < ONCOLOGY

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4 **Prognostic risk factor analysis and construction of a nomogram for elderly**  
5 **primary liver cancer patients based on SEER database**  
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43 **Running title:** Nomogram model for primary liver cancer in elderly patients  
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46 **Key words:** nomogram, primary liver cancer, elderly, database  
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## Abstract

**Objective:** To evaluate the risk factors and construct a nomogram model for the prognosis of primary liver cancer in the elderly based on the data from the US SEER database. **Methods:** The latest data of primary liver cancer patients were extracted from the SEER database with SEER\*STAT software, and the required variables were included. The data was screened and then divided into training cohort and validation cohort. Variates were first screened by univariate and multivariate COX analysis, and variates with then statistical significance were included the construction of a nomogram model. The C-Index, ROC and calibration curves were used to evaluate the model. **Results:** A total of 10824 eligible cases from 2004 to 2017 were extracted, among which, 7757 cases were included in the training cohort and 3247 in the validation cohort. The C-Index of the model was 0.747 (training cohort) and 0.773 (validation cohort). The 3-year AUCs of the training and validation cohort were 0.760 and 0.750, while the 5-year AUCs were 0.761 and 0.748. The calibration curves showed an ideal calibration of the constructed model. **Conclusions:** The nomogram model constructed followed by COX regression analysis showed ideal calibration and discrimination property, and can provide a reference for clinical application of elderly primary liver cancer in the future.

### Strength and limitations of this study:

#### Strength:

1. Collected a large and sufficient number of cases from SEER database of elderly liver cancer.
2. Constructed a novel and ideal prognostic model for elderly liver cancer

**Limitations:**

- 1.All cases were collected form one database and selection bias might exist.
- 2.Some classification carried out by SEER database was not very specific.
- 3.Information such as ancillary tests was absent from the SEER database.

**Keywords:** nomogram, primary liver cancer, elderly, database

**Introduction**

Primary liver cancer is currently the sixth most common cancer worldwide and, according to epidemiological surveys, is the fourth leading cause of cancer-related deaths globally, representing a major threat to the health of the entire human population <sup>[1,2]</sup>. Furthermore, many studies have pointed out that although middle-aged (30-59 years old) or young (< 30 years old) patients with primary liver cancer are not uncommon worldwide, the average age of diagnosis of the disease is 60 years old and, in contrast to the yearly decrease in the age-standardized incidence rate (ASR) of young patients, the incidence of elderly patients has continuously increased in more than half of



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4 the countries and regions during the last 30 years [3-5]. The global population expansion, increasing  
5 aging, as well as obesity, diabetes, overmedication and lagging effects of HBV infection in the  
6 elderly may be responsible for the high or even increasing ASR of primary liver cancer in elderly  
7 patients, creating a heavy burden on the health of all countries [6-8]. In terms of treatment, surgery  
8 remains the first choice for primary liver cancer. Therefore, based on the epidemiological  
9 characteristics and treatment modalities of the disease, it is necessary to conduct an accurate  
10 prognostic assessment of elderly patients with primary liver cancer to guide clinical work.  
11 However, the different pathological types and heterogeneity of the disease make prognostic  
12 assessment still difficult.  
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22 Recently, the nomogram model has shown superior predictive performance over the  
23 traditional TNM staging because of its convenient modeling method and the ability to incorporate  
24 multiple variables, thus gaining widespread popularity [9,10]. This study intended to use a  
25 nomogram model to analyze the risk factors affecting elderly primary liver cancer in the SEER  
26 database and to predict the prognosis of the disease. The assessment performance of the model  
27 was analyzed by the test of discrimination and calibration to establish an optimal assessment  
28 system for clinical work such as the treatment of elderly primary liver cancer.  
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## 39 **Methods and data**

### 40 41 42 43 44 1. Ethical statement

45  
46 Informed consent was not required from patients to obtain data from the US SEER database  
47 since cancer is publicly reportable in every state in the United States.  
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### 50 51 2. Patient and Public Involvement

52  
53 No patient involved.  
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### 56 3. Case selection

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58 Case data of primary liver cancer with complete follow-up records were selected from the  
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2004-2017 SEER database (SEER research data, 18 Registries, Nov 2019 Sub (2000-2017)) using SEER\*Stat 8.3.6.

Inclusion criteria:

1. Ethnic groups are Asian, Pacific Islanders, American Indians and Alaskans.
2. The main site of primary liver cancer is liver or intrahepatic bile duct (IBD).
3. The histological types of primary liver cancer are intrahepatic cholangiocarcinoma (ICC), hepatocellular carcinoma (HCC) and associated liver cancer (CHC).

Exclusion criteria:

1. For patients under 65 years old.
2. For incomplete follow-up records.
3. Non-tumor-related death.

The extracted variables included race, year of diagnosis, age, sex, primary site, histologic type, grade, TNM stage, tumor size, surgery on the primary site (included photodynamic therapy (PDT), percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA), etc.), survival time, cause of death and survival status. Among them, patients who were older than 65 years old were selected; Asian and Pacific Islanders, American Indians and Alaskan natives were included in Asian and others for the race variable; liver or intrahepatic bile duct (IBD) was selected as the primary site; intrahepatic cholangiocarcinoma (ICC), hepatocellular carcinoma (HCC), and combined hepatic carcinoma (CHC) were selected as the histologic type.

#### 4. Statistical processing

The survival endpoint and survival time were defined as 3 years and 5 years, separately. Using X-Tile software, through the "enumeration method", that is, the statistical test is carried out by grouping different values as cut-off values, the result with the smallest p value can be considered as the best cut-off value. It is concluded that the variables of high, medium and low risk are divided into < 46mm, 46-81mm and > 81mm respectively.. After that, the total cases were randomly assigned to a training or a validation cohort at a ratio of 7:3 using SPSS 18.0 by random

number 20200222, followed by the collection of baseline information. Univariate and multivariate (Forward: LR) COX analyses were performed using the R software or SPSS to screen for statistically significant variables to construct a nomogram, based on which C-Index, ROC curves and the area under the curve (AUC) were figured out. Calibration curves of the model for 3 and 5 years were plotted with the R software after Bootstrap sampling for 1000 times.  $P < 0.05$  was considered statistically significant.

## Results

### 1. Clinical characteristics of the cases

A total of 10,824 elderly cases with primary liver cancer were extracted in accordance with screening conditions, with 7,757 included in the training cohort and 3,247 in the validation one. Among them, the majority of patients were male (67.5%), white (71.3%), with primary site in the liver (87.8%), HCC (84.7%), grade II (46.6%), T1 (46.5%), N0 (91.6%), M0 (88.7%) and unoperated (56.5%) (Table 1).

**Table 1** Baseline data of extracted cases

Variates	Total cohort 10824(100%)	Training cohort 7577(100%)	Validation cohort 3247(100%)
<b>Age</b>			
65-69	3600(33.3%)	2540(33.5%)	1060(32.6%)
70-74	2829(26.1%)	1994(26.3%)	835(25.7%)
75-79	2228(20.6%)	1544(20.4%)	684(21.1%)
80-84	1451(13.4%)	1001(13.2%)	450(13.9%)
>84	716(6.61%)	498(6.57%)	218(6.71%)
<b>Sex</b>			
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Female	3515(32.5%)	2455(32.4%)	1060(32.6%)
<b>Race</b>			
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Black	956(8.83%)	672(8.87%)	284(8.75%)
Asian or others	2146(19.8%)	1515(20.0%)	631(19.4%)
<b>Primary site</b>			
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IBD	1316(12.2%)	903(11.9%)	413(12.7%)
<b>Histological type</b>			
HCC	9171(84.7%)	6419(84.7%)	2752(84.8%)
ICC	1570(14.5%)	1095(14.5%)	475(14.6%)
CHC	83(0.77%)	63(0.83%)	20(0.62%)
<b>Grade</b>			
I	3108(28.7%)	2163(28.5%)	945(29.1%)
II	5040(46.6%)	3510(46.3%)	1530(47.1%)
III	2504(23.1%)	1785(23.6%)	719(22.1%)
IV	172(1.59%)	119(1.57%)	53(1.63%)
<b>T</b>			
T1	5028(46.5%)	3523(46.5%)	1505(46.4%)
T2	2547(23.5%)	1786(23.6%)	761(23.4%)
T3	2765(25.5%)	1932(25.5%)	833(25.7%)
T4	484(4.47%)	336(4.43%)	148(4.56%)
<b>N</b>			
N0	9910(91.6%)	6931(91.5%)	2979(91.7%)
N1	914(8.44%)	646(8.53%)	268(8.25%)
<b>M</b>			
M0	9605(88.7%)	6716(88.6%)	2889(89.0%)

M1	1219(11.3%)	861(11.4%)	358(11.0%)
<b>Surgery</b>			
Resection	1901(17.5%)	1315(17.4%)	586(18.0%)
Lobectomy	1116(10.3%)	807(10.7%)	309(9.52%)
Transplantation	328(3.03%)	238(3.14%)	90(2.77%)
Destruction	1087(10.0%)	769(10.1%)	318(9.79%)
Extended resection	277(2.56%)	195(2.56%)	82(2.53%)
None	6115(56.5%)	4253(56.1%)	1862(57.3%)
<b>Tumor size(mm):</b>			
<46	4168(38.5%)	2925(38.6%)	1243(38.3%)
46-81	3532(32.6%)	2491(32.9%)	1041(32.1%)
>81	3124(28.9%)	2161(28.5%)	963(29.7%)

## 2. Screening for prognostic risk factors

Univariate COX regression analysis of the training cohort proved the variates of age, sex, race, histological type, grade, TNM stage, surgery and tumor size to be statistically significant ( $P < 0.05$ ), which were included in the follow-up multivariate COX analysis. However, the primary site was excluded according to the analysis ( $P = 0.232$ ) (Table 2). Subsequently, the sex variable was further excluded from the experiment by Forward: LR multivariate COX (Table 3). In conclusion, age, race, histological type, grade, TNM stage, surgery, and tumor size were independent risk factors that affect the prognosis of elderly patients from the extracted data with primary liver cancer, which could be used to construct a subsequent nomogram prediction model.

**Table 2** Univariate COX analysis

Variates	P-value	Hazard ratio	95%CI	
			lower	upper
<b>Age</b>	<b>&lt;0.001</b>			

65-69	Reference			
70-74	<0.001	1.168	1.085	1.257
75-79	<0.001	1.420	1.314	1.534
80-84	<0.001	1.639	1.502	1.788
>84	<0.001	2.072	1.855	2.314
<b>Sex</b>	<b>0.003</b>			
Male	Reference			
Female	0.003	0.914	0.862	0.969
<b>Race</b>	<b>&lt;0.001</b>			
White	Reference			
Black	0.224	1.062	0.964	1.170
Asian or others	<0.001	0.737	0.685	0.792
<b>Primary site</b>	<b>0.232 (Excluded)</b>			
Liver	Reference			
IBD	0.232	1.055	0.967	1.151
<b>Histological type</b>	<b>0.032</b>			
HCC	Reference			
ICC	0.383	0.881	0.663	1.171
CHC	0.861	0.974	0.727	1.305
<b>Grade</b>	<b>&lt;0.001</b>			
I	Reference			
II	0.043	0.934	0.875	0.998
III	<0.001	1.464	1.360	1.577
IV	0.001	1.437	1.162	1.776
<b>T</b>	<b>&lt;0.001</b>			
T1	Reference			
T2	<0.001	1.213	1.129	1.304

T3	<0.001	2.446	2.290	2.614
T4	<0.001	2.493	2.200	2.825
<b>N</b>	<b>&lt;0.001</b>			
N0	Reference			
N1	<0.001	2.265	2.072	2.476
<b>M</b>	<b>&lt;0.001</b>			
M0	Reference			
M1	<0.001	3.025	2.798	3.271
<b>Surgery</b>	<b>&lt;0.001</b>			
Resection	Reference			
Lobectomy	<0.001	0.234	0.213	0.256
Transplantation	<0.001	0.268	0.241	0.299
Destruction	<0.001	0.079	0.060	0.104
Extended resection	<0.001	0.366	0.332	0.403
None	<0.001	0.372	0.308	0.449
<b>Tumor size(mm):</b>	<b>&lt;0.001</b>			
<46	Reference			
46-81	<0.001	1.744	1.630	1.867
>81	<0.001	2.577	2.405	2.761

CI: confidence interval.

**Table 3** Multivariates COX analysis

Variates	P-value	Hazard ratio	95%CI	95%CI
			lower	upper
<b>Age</b>				
65-69	Reference			
70-74	0.029	1.086	1.009	1.170

75-79	<0.001	1.219	1.127	1.318
80-84	<0.001	1.307	1.196	1.428
>84	<0.001	1.484	1.326	1.660
<b>Sex</b>	<b>(Excluded)</b>			
Male				
Female				
<b>Race</b>				
White	Reference			
Black	0.325	1.051	0.952	1.159
Asian or others	<0.001	0.813	0.756	0.875
<b>Histological type</b>				
HCC	Reference			
ICC	0.159	0.940	0.863	1.024
CHC	0.005	1.508	1.132	2.010
<b>Grade</b>				
I	Reference			
II	0.001	1.121	1.047	1.199
III	<0.001	1.567	1.449	1.695
IV	<0.001	1.683	1.358	2.086
<b>T</b>				
T1	Reference			
T2	<0.001	1.282	1.190	1.381
T3	<0.001	1.542	1.435	1.657
T4	<0.001	1.689	1.484	1.923
<b>N</b>				
N0	Reference			
N1	<0.001	1.253	1.136	1.382



<b>M</b>				
M0	Reference			
M1	<0.001	1.556	1.429	1.694
<b>Surgery</b>				
Resection	Reference			
Lobectomy	0.833	1.014	0.889	1.157
Transplantation	<0.001	0.417	0.313	0.557
Destruction	<0.001	1.851	1.632	2.100
Extended resection	0.007	1.325	1.080	1.626
None	<0.001	3.552	3.229	3.906
<b>Tumor size(mm):</b>				
<46	Reference			
46-81	<0.001	1.291	1.199	1.391
>81	<0.001	1.597	1.474	1.730

CI: confidence interval.

### 3. Nomogram model construction and verification

The independent risk factors affecting prognosis derived from the above analysis were incorporated to construct a 3- and 5-year nomogram prediction model for elderly primary liver cancer, and the total score was calculated by aggregating the scores of each variable to predict the survival rate of patients at 3 and 5 years (Figure 1). It can be seen that the surgery on the primary site was the most important factor affecting the score in this model, followed by tumor size, TNM stage and age. The AUC was calculated after plotting the ROC curves of the training and validation cohorts. Specifically, the AUC is 0.760 (3 years) and 0.761 (5 years) in the training cohort and 0.750 (3 years) and 0.748 (5 years) in the validation cohort (Figure 2). Furthermore, the model showed an ideal calibration for 3 and 5 years in both groups after creating the calibration curves for the training and validation cohorts (Figure 3). The comparison of predictive value between 3-years nomogram model and TNM model was with an AUC of 0.758 and 0.698 (P

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4 <0.05) separately, and between 5-years nomogram model and TNM model was with an AUC of  
5 0.750 and 0.609 (P <0.01), respectively (Figure 4).  
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## 10 **Discussion**

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16 Analysis of cases revealed that male patients accounted for more than 60% of elderly patients  
17 with primary liver cancer. Some statistics have presented that the mean annual change rate of men  
18 suffering from the disease is higher than that of women (3.7% vs. 2.7%) in the United States [11].  
19 In China, a population-based study of hepatic carcinoma in Zhejiang Province demonstrated that  
20 the ASR for hepatic carcinoma was 33.24 in men compared to 1.21 in women [12]. Not only  
21 differences in lifestyle---including alcohol consumption and smoking---have led to higher cancer  
22 rates in men, but different physiological conditions such as hormone secretion and even genetic  
23 differences may be responsible for these epidemiological differences [13]. Therefore, it has been  
24 put forward that gender is a critical biological variable that should be considered in all studies  
25 aimed at improving carcinoma [14]. Analysis of baseline data also suggested that the population of  
26 elderly primary liver cancer was predominantly white and mostly with the primary site in the liver,  
27 HCC histological type, grade II (moderately differentiated), T1 and without lymph node  
28 metastasis or distant metastasis. Moreover, in this population, more than half of the cases were not  
29 treated surgically. The reason for this phenomenon may be that most of the patients were over 60  
30 years old at the time of diagnosis, missing the best timing for radical surgery, together with the  
31 decline in physical function as well as intolerance to surgery led to a palliative treatment for most  
32 patients.  
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50 Based on further univariate and multivariate COX analyses, several independent risk factors  
51 that affect the prognosis of the disease were sifted out, including age, race, histological type,  
52 grade, TNM stage, surgery and tumor size. Sex, though not negligible as previously mentioned,  
53 was found not to be the main factor affecting prognosis in this population after comprehensive  
54 analysis, which is consistent with several current retrospective studies on hepatic carcinoma  
55 [15-17]. Some clinical information affecting the operation, such as metastatic cancer, can be  
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4 reflected in the TNM staging. In terms of histological type, it is evident that CHC has a worse  
5 prognosis than the common HCC, which shows a lower incidence but a higher malignancy [18-19].  
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7 Analysis of the age factor revealed that the higher the age group of the patient, the worse the  
8 prognosis, suggesting a linear negative correlation trend. The nomogram model also indicated  
9 that the surgery option was the most crucial factor influencing the prognosis of the disease. The  
10 patients who underwent liver transplantation, though small in number, showed a relatively good  
11 prognosis, followed by resection or lobectomy and then by local destruction. In contrast, patients  
12 without surgery showed a poor prognosis. This factor alone reduced the 3- and 5-year predicted  
13 survival rates to less than 50%, suggesting that the invention of new methods or enhanced  
14 surgery is still an urgent issue for improving the prognosis of elderly primary liver cancer. The  
15 influence of other factors on prognosis is basically in line with the current consensus that the  
16 worse the grade, the higher the T-stage, the occurrence of lymph node metastasis, the occurrence  
17 of distant metastasis and the larger the tumor, the worse the prognosis of the patient.  
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30 After that, the performance of the established model was evaluated by C-Index, ROC  
31 curves and calibration curves. A nomogram model is considered to have good discrimination if  
32 its C-Index and AUC exceed 0.7 [20,21]. As the model constructed in this study had these two  
33 indicators above 0.7 in both the training and validation cohorts and the calibration plots scatter in  
34 accordance with the reference line, it could be considered that the model has good discrimination  
35 and calibration and hence the capacity to predict the prognosis of the disease.  
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42 However, this study also has shortcomings. First, the cases were all from the US SEER  
43 database, which is not representative of regions other than the United States and is subject to  
44 selection bias. In addition, the case data included in this database lacked some important  
45 ancillary tests related to the diagnosis and treatment of liver cancer, such as CEA, AST and  
46 vascular invasion. More importantly, the radiotherapy and chemotherapy information contained  
47 in this database can only be obtained by signing some agreements, which can not be obtained for  
48 the time being, so we are unable to study the relationship between radiotherapy, chemotherapy,  
49 targeted therapy and the prognosis of liver cancer [22].  
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58 In conclusion, a nomogram model with favorable prediction was developed by using the  
59 case data from the SEER database after performing univariate and multivariate COX screening,  
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4 which could provide a reference for the future diagnosis and treatment of elderly patients with  
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6 primary liver cancer.  
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### 10 **Funding**

11  
12  
13 This research received no specific grant from any funding agency in the public, commercial or  
14  
15 not-for-profit sectors.  
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### 18 **Conflicts of interest**

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21 The authors declare there are no competing interests.  
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### 28 **Author contributions**

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31 Fangyuan Li wrote and revised the manuscript; Ting Zheng conducted most of the analysis of  
32  
33 data; Xuewei Gu reviewed the manuscript; All authors read and approved the final manuscript.  
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### 38 **Availability of data and material**

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41 The datasets used and/or analyzed during the current study are available from the corresponding  
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43 author on reasonable request.  
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### 50 **Ethics approval and consent to participate**

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53 Informed consent was not required from patients to obtain data from the US SEER database since  
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55 cancer is publicly reportable in every state in the United States.  
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### 33 **Figure Legends**

34  
35 **Figure 1** Constructed nomogram  
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38 **Figure 2** 3- and 5-year survival ROC curves for the training and validation cohorts. A: 3-year  
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40 survival ROC curve for the training cohort. B: 5-year survival ROC curve for the training cohort.  
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42 C: 3-year survival ROC curve for the validation cohort. D: 5-year survival ROC curve for the  
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44 validation cohort.  
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47 **Figure 3** 3- and 5-year survival calibration curves for the training and validation cohorts. A:  
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49 3-year survival calibration curve for the training cohort. B: 5-year survival calibration curve for  
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51 the training cohort. C: 3-year survival calibration curve for the validation cohort. D: 5-year  
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53 survival calibration curve for the validation cohort.  
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55 **Figure.4** The comparison of ROC between nomogram model and TNM model. (A: 3-years  
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57 nomogram model, B: 5-years nomogram model)  
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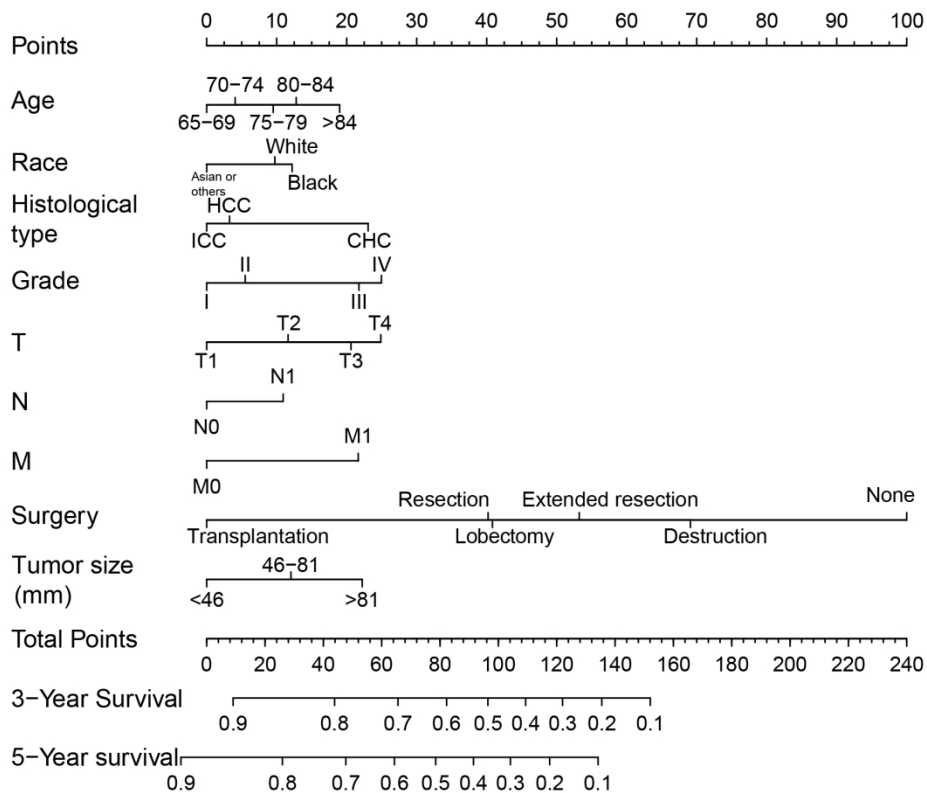


Figure 1 Constructed nomogram



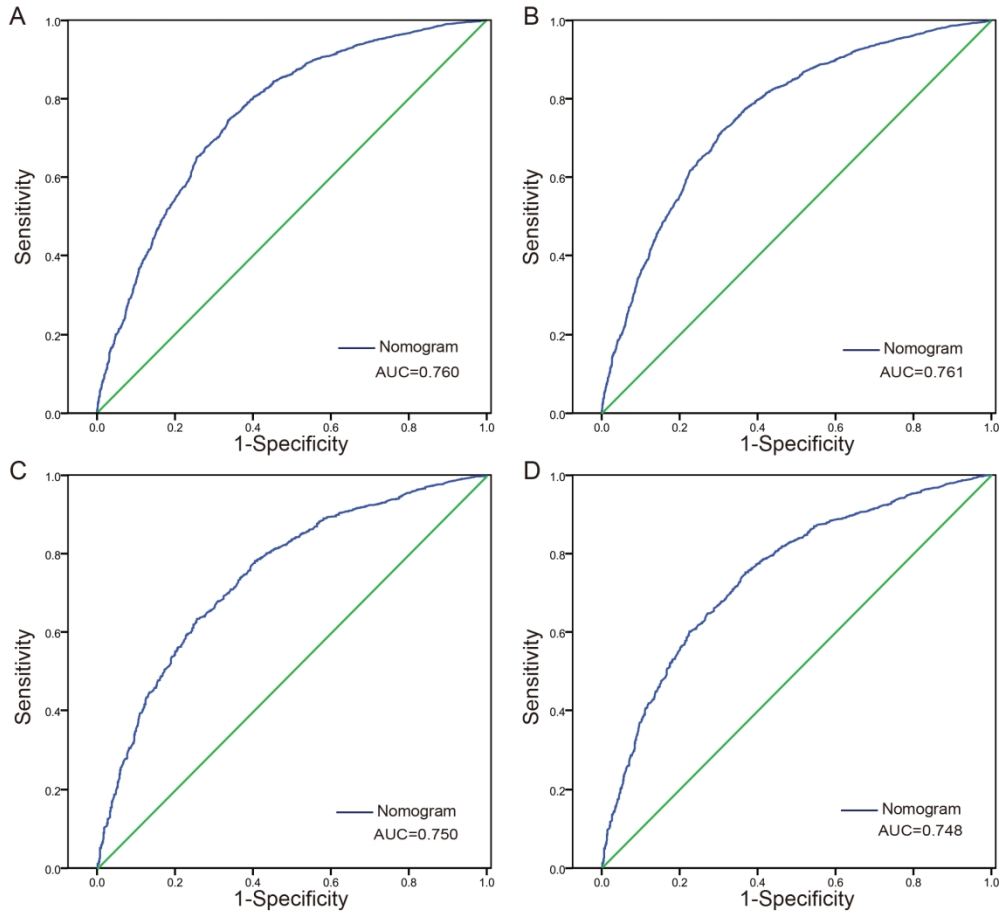


Figure 2 3- and 5-year survival ROC curves for the training and validation cohorts. A: 3-year survival ROC curve for the training cohort. B: 5-year survival ROC curve for the training cohort. C: 3-year survival ROC curve for the validation cohort. D: 5-year survival ROC curve for the validation cohort.

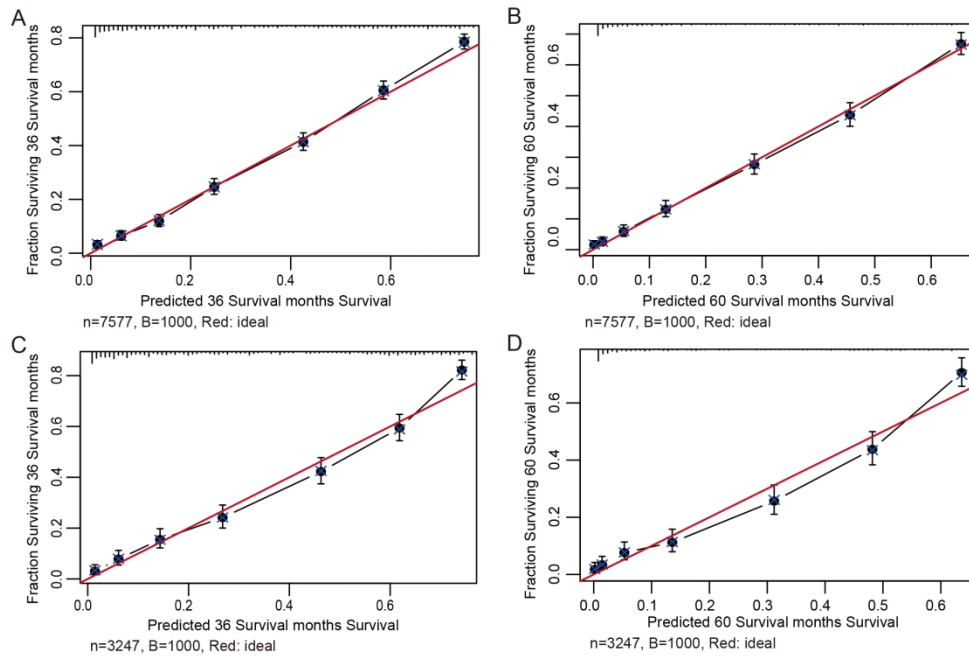


Figure 3 3- and 5-year survival calibration curves for the training and validation cohorts. A: 3-year survival calibration curve for the training cohort. B: 5-year survival calibration curve for the training cohort. C: 3-year survival calibration curve for the validation cohort. D: 5-year survival calibration curve for the validation cohort.

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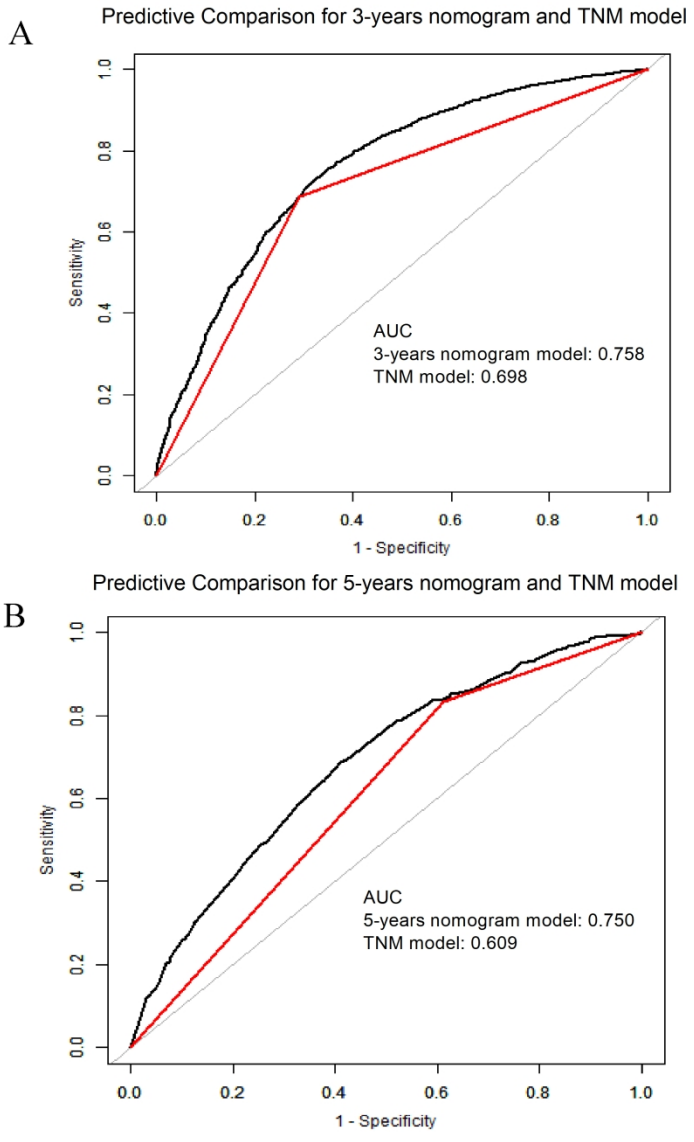


Figure.4 The comparison of ROC between nomogram model and TNM model. (A: 3-years nomogram model, B: 5-years nomogram model)

203x291mm (300 x 300 DPI)

**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology\***  
**Checklist for cohort, case-control, and cross-sectional studies (combined)**

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	5

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Prognostic risk factor analysis and nomogram construction for primary liver cancer in elderly patients based on SEER database

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4 **Prognostic risk factor analysis and nomogram construction for primary liver**  
5 **cancer in elderly patients based on SEER database**  
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43 **Running title:** Nomogram model for primary liver cancer in elderly patients  
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46 **Key words:** nomogram, primary liver cancer, elderly, database  
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## Abstract

**Objective:** To evaluate the risk factors and construct a nomogram model for the prognosis of primary liver cancer in the elderly based on the data from the US SEER database. **Methods:** The latest data of patients with primary liver cancer were extracted from the SEER database using SEER\*STAT software, and the required variables were included. The data were screened and then divided into a training cohort and a validation cohort. A nomogram model was constructed by screening the variables through univariate and multivariate COX analysis. The C-Index, ROC, and calibration curves were used for model evaluation. **Results:** A total of 10824 eligible cases from 2004 to 2017 were extracted, among which, 7757 cases were included in the training cohort and 3247 in the validation cohort. The C-Index of the model was 0.747 (in the training cohort) and 0.773 (in the validation cohort). The 3-year AUCs of the training and the validation cohorts were 0.760 and 0.750, and the 5-year AUCs of the two cohorts were 0.761 and 0.748. The calibration curves showed an ideal calibration of the constructed model. **Conclusions:** The nomogram model constructed followed by COX regression analysis showed moderate calibration and discrimination property, and can provide reference to a certain extent for future clinical application of primary liver cancer in the elderly.

### Strengths and limitations of this study:

#### Strengths:

1. A large and sufficient number of elderly cases with liver cancer were collected from the SEER database.
2. A novel and ideal prognostic model was constructed for the elderly patients with liver cancer.

**Limitations:**

1. Selection bias might exist, because all the cases were retrieved from the same database.
2. Some of the classifications carried out in the SEER database were not specific enough.
3. Information such as ancillary tests were absent from the SEER database.

**Keywords:** nomogram, primary liver cancer, elderly, database

**Introduction**

Primary liver cancer is currently the sixth most common cancer worldwide, and is the fourth leading cause of cancer-related deaths globally according to epidemiological surveys, posing a major threat to the health of the entire human population <sup>[1,2]</sup>. Furthermore, many studies have pointed out that although middle-aged (30-59 years old) or young (< 30 years old) patients with primary liver cancer are not uncommon worldwide, the average age of diagnosis of the disease is 60. Besides, in contrast to the yearly decrease of the age-standardized incidence rate (ASR) among young patients, the incidence in elderly patients has continuously increased in more than half of the

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3 countries and regions during the last 30 years [3-5]. Global population expansion, increasing aging,  
4 as well as obesity, diabetes, overmedication and lagging effects of HBV infection in the elderly may  
5 be responsible for the high or even increased ASR in elderly patients with primary liver cancer,  
6 imposing a heavy burden on the health sectors of all countries [6-8]. Surgery remains the first choice  
7 for the treatment of primary liver cancer. Therefore, based on the epidemiological characteristics  
8 and treatment modalities of primary liver cancer, it is necessary to accurately assess the prognosis  
9 of the disease in elderly patients for the guide of clinical practice. However, different pathological  
10 types and heterogeneity of the disease still make its prognostic assessment difficult.  
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20 Recently, the nomogram model has gained widespread popularity due to its superior predictive  
21 performance over the traditional TNM staging in the aspects of its convenient modeling method and  
22 ability to incorporate multiple variables [9,10]. This study intended to construct a nomogram model  
23 to analyze the risk factors of primary liver cancer in elderly patients base on the SEER database and  
24 to predict the prognosis of the disease. The evaluation effect of the model was analyzed by the test  
25 of discrimination and calibration, through which an optimal assessment system was established for  
26 the clinical practice such as the treatment of elderly patients with primary liver cancer.  
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## 37 **Methods and data**

### 38 1. Ethical statement

39 Informed consent was not required from patients to obtain data from the US SEER database  
40 since cancer is publicly reportable in every state in the United States.  
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### 44 2. Patient and public involvement

45 No patient involved.  
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### 49 3. Case selection

50 Case data of primary liver cancer with complete follow-up records were selected from the  
51 2004-2017 SEER database (SEER research data, 18 Registries, Nov 2019 Sub (2000-2017)) using  
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4 SEER\*Stat 8.3.6.  
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6 Inclusion criteria:  
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9 1. Ethnic groups are Asians, Pacific Islanders, American Indians and Alaskans.  
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11 2. The main site of primary liver cancer is liver or intrahepatic bile duct (IBD).  
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13 3. The histological types of primary liver cancer are intrahepatic cholangiocarcinoma (ICC),  
14 hepatocellular carcinoma (HCC) and associated liver cancer (CHC).  
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18 Exclusion criteria:  
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21 1. For patients under 65 years old.  
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23 2. For incomplete follow-up records.  
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25 3. Non-tumor-related death.  
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29 Race, year of diagnosis, age, sex, primary site, histologic type, grade, TNM stage, tumor size,  
30 surgery on the primary site (including photodynamic therapy (PDT), percutaneous ethanol injection  
31 (PEI) and radiofrequency ablation (RFA), etc.), survival time, cause of death and survival status  
32 were all extracted variables. Among them, patients over 65 years old were selected; Asians and  
33 Pacific Islanders, American Indians and Alaskan natives were included as the race variable of  
34 Asians and others; liver or intrahepatic bile duct (IBD) was selected as the primary site; intrahepatic  
35 cholangiocarcinoma (ICC), hepatocellular carcinoma (HCC), and combined hepatic carcinoma  
36 (CHC) were selected as the histologic type.  
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#### 45 4. Statistical processing 46 47

48 The survival endpoint and survival time were defined as 3 years and 5 years, separately. The  
49 statistical test is carried out by grouping different values as cut-off values through the “enumeration  
50 method” using X-Tile software, and the result with the smallest p value can be considered as the  
51 best cut-off value. It was concluded that the variables of high, medium and low risks are divided  
52 into < 46mm, 46-81mm and > 81mm respectively. After that, all the cases were randomly assigned  
53 to a training or a validation cohort at a ratio of 7:3 using SPSS 18.0 by random number 20200222,  
54 followed by the collection of baseline information. Univariate and multivariate (Forward: LR) COX  
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analyses were performed using the R software or SPSS to screen statistically significant variables for nomogram construction, based on which, C-Index, ROC curves and the area under the curve (AUC) were figured out. Calibration curves of the model for 3 and 5 years were plotted with the R software after Bootstrap sampling for 1000 times.  $P < 0.05$  was considered statistically significant.

## Results

### 1. Clinical characteristics of the cases

A total of 10,824 elderly cases with primary liver cancer were extracted in accordance with the screening conditions, including 7,757 in the training cohort and 3,247 in the validation one. Among them, the majority of patients were male (67.5%), white (71.3%), with primary site in the liver (87.8%), HCC (84.7%), grade II (46.6%), T1 (46.5%), N0 (91.6%), M0 (88.7%) and unoperated (56.5%) (Table 1).

**Table 1** Baseline data of the extracted cases

Variates	Total cohort 10824(100%)	Training cohort 7577(100%)	Validation cohort 3247(100%)
<b>Age</b>			
65-69	3600(33.3%)	2540(33.5%)	1060(32.6%)
70-74	2829(26.1%)	1994(26.3%)	835(25.7%)
75-79	2228(20.6%)	1544(20.4%)	684(21.1%)
80-84	1451(13.4%)	1001(13.2%)	450(13.9%)
>84	716(6.61%)	498(6.57%)	218(6.71%)
<b>Sex</b>			
Male	7309(67.5%)	5122(67.6%)	2187(67.4%)
Female	3515(32.5%)	2455(32.4%)	1060(32.6%)
<b>Race</b>			
White	7722(71.3%)	5390(71.1%)	2332(71.8%)
Black	956(8.83%)	672(8.87%)	284(8.75%)
Asian or others	2146(19.8%)	1515(20.0%)	631(19.4%)
<b>Primary site</b>			
Liver	9508(87.8%)	6674(88.1%)	2834(87.3%)

IBD	1316(12.2%)	903(11.9%)	413(12.7%)
<b>Histological type</b>			
HCC	9171(84.7%)	6419(84.7%)	2752(84.8%)
ICC	1570(14.5%)	1095(14.5%)	475(14.6%)
CHC	83(0.77%)	63(0.83%)	20(0.62%)
<b>Grade</b>			
I	3108(28.7%)	2163(28.5%)	945(29.1%)
II	5040(46.6%)	3510(46.3%)	1530(47.1%)
III	2504(23.1%)	1785(23.6%)	719(22.1%)
IV	172(1.59%)	119(1.57%)	53(1.63%)
<b>T</b>			
T1	5028(46.5%)	3523(46.5%)	1505(46.4%)
T2	2547(23.5%)	1786(23.6%)	761(23.4%)
T3	2765(25.5%)	1932(25.5%)	833(25.7%)
T4	484(4.47%)	336(4.43%)	148(4.56%)
<b>N</b>			
N0	9910(91.6%)	6931(91.5%)	2979(91.7%)
N1	914(8.44%)	646(8.53%)	268(8.25%)
<b>M</b>			
M0	9605(88.7%)	6716(88.6%)	2889(89.0%)
M1	1219(11.3%)	861(11.4%)	358(11.0%)
<b>Surgery</b>			
Resection	1901(17.5%)	1315(17.4%)	586(18.0%)
Lobectomy	1116(10.3%)	807(10.7%)	309(9.52%)
Transplantation	328(3.03%)	238(3.14%)	90(2.77%)
Destruction	1087(10.0%)	769(10.1%)	318(9.79%)
Extended resection	277(2.56%)	195(2.56%)	82(2.53%)
None	6115(56.5%)	4253(56.1%)	1862(57.3%)
<b>Tumor size(mm):</b>			
<46	4168(38.5%)	2925(38.6%)	1243(38.3%)
46-81	3532(32.6%)	2491(32.9%)	1041(32.1%)
>81	3124(28.9%)	2161(28.5%)	963(29.7%)

## 2. Screening for prognostic risk factors

Univariate COX regression analysis were performed on the training cohort, and the variates of age, sex, race, histological type, grade, TNM stage, surgery and tumor size were proved to be

statistically significant ( $P < 0.05$ ) and included in the follow-up multivariate COX analysis. However, the primary site was excluded according to the analysis ( $P = 0.232$ ) (Table 2). Subsequently, the variable of sex was further excluded from the experiment by Forward: LR multivariate COX (Table 3). In the end, age, race, histological type, grade, TNM stage, surgery, and tumor size were all independent risk factors affecting the prognosis of elderly patients with primary liver cancer, and could be used for constructing nomogram prediction model.

**Table 2** Univariate COX analysis

Variates	P-value	Hazard ratio	95%CI lower	95%CI upper
<b>Age</b>	<b>&lt;0.001</b>			
65-69	Reference			
70-74	<0.001	1.168	1.085	1.257
75-79	<0.001	1.420	1.314	1.534
80-84	<0.001	1.639	1.502	1.788
>84	<0.001	2.072	1.855	2.314
<b>Sex</b>	<b>0.003</b>			
Male	Reference			
Female	0.003	0.914	0.862	0.969
<b>Race</b>	<b>&lt;0.001</b>			
White	Reference			
Black	0.224	1.062	0.964	1.170
Asian or others	<0.001	0.737	0.685	0.792
<b>Primary site</b>	<b>0.232 (Excluded)</b>			
Liver	Reference			
IBD	0.232	1.055	0.967	1.151
<b>Histological type</b>	<b>0.032</b>			
HCC	Reference			
ICC	0.383	0.881	0.663	1.171
CHC	0.861	0.974	0.727	1.305
<b>Grade</b>	<b>&lt;0.001</b>			
I	Reference			
II	0.043	0.934	0.875	0.998
III	<0.001	1.464	1.360	1.577
IV	0.001	1.437	1.162	1.776
<b>T</b>	<b>&lt;0.001</b>			

T1	Reference			
T2	<0.001	1.213	1.129	1.304
T3	<0.001	2.446	2.290	2.614
T4	<0.001	2.493	2.200	2.825
<b>N</b>	<b>&lt;0.001</b>			
N0	Reference			
N1	<0.001	2.265	2.072	2.476
<b>M</b>	<b>&lt;0.001</b>			
M0	Reference			
M1	<0.001	3.025	2.798	3.271
<b>Surgery</b>	<b>&lt;0.001</b>			
Resection	Reference			
Lobectomy	<0.001	0.234	0.213	0.256
Transplantation	<0.001	0.268	0.241	0.299
Destruction	<0.001	0.079	0.060	0.104
Extended resection	<0.001	0.366	0.332	0.403
None	<0.001	0.372	0.308	0.449
<b>Tumor size(mm):</b>	<b>&lt;0.001</b>			
<46	Reference			
46-81	<0.001	1.744	1.630	1.867
>81	<0.001	2.577	2.405	2.761

CI: confidence interval.

**Table 3** Multivariates COX analysis

Variates	P-value	Hazard ratio	95%CI lower	95%CI upper
<b>Age</b>				
65-69	Reference			
70-74	0.029	1.086	1.009	1.170
75-79	<0.001	1.219	1.127	1.318
80-84	<0.001	1.307	1.196	1.428
>84	<0.001	1.484	1.326	1.660
<b>Sex</b>	<b>(Excluded)</b>			
Male				
Female				
<b>Race</b>				
White	Reference			



Black	0.325	1.051	0.952	1.159
Asian or others	<0.001	0.813	0.756	0.875
<b>Histological type</b>				
HCC	Reference			
ICC	0.159	0.940	0.863	1.024
CHC	0.005	1.508	1.132	2.010
<b>Grade</b>				
I	Reference			
II	0.001	1.121	1.047	1.199
III	<0.001	1.567	1.449	1.695
IV	<0.001	1.683	1.358	2.086
<b>T</b>				
T1	Reference			
T2	<0.001	1.282	1.190	1.381
T3	<0.001	1.542	1.435	1.657
T4	<0.001	1.689	1.484	1.923
<b>N</b>				
N0	Reference			
N1	<0.001	1.253	1.136	1.382
<b>M</b>				
M0	Reference			
M1	<0.001	1.556	1.429	1.694
<b>Surgery</b>				
Resection	Reference			
Lobectomy	0.833	1.014	0.889	1.157
Transplantation	<0.001	0.417	0.313	0.557
Destruction	<0.001	1.851	1.632	2.100
Extended resection	0.007	1.325	1.080	1.626
None	<0.001	3.552	3.229	3.906
<b>Tumor size(mm):</b>				
<46	Reference			
46-81	<0.001	1.291	1.199	1.391
>81	<0.001	1.597	1.474	1.730

CI: confidence interval.

### 3. Nomogram model construction and verification

The 3- and 5-year nomogram prediction model for primary liver cancer in the early were constructed based on the independent risk factors affecting the prognosis of the disease derived from the above analysis. The total score was calculated by aggregating the scores of each variable to

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4 predict the 3- and 5- year survival rate of patients (Figure 1). It can be seen that the most important  
5 factor affecting the score in this model was surgery on the primary site, followed by tumor size,  
6 TNM stage and age. The AUC was calculated after plotting the ROC curves of the training and the  
7 validation cohorts. Specifically, the AUC is 0.760 (3 years) and 0.761 (5 years) in the training cohort,  
8 and 0.750 (3 years) and 0.748 (5 years) in the validation cohort (Figure 2). Furthermore, the model  
9 showed an ideal calibration for 3- and 5- year survival prediction in both groups after creating the  
10 calibration curves for the training and the validation cohorts (Figure 3). By comparing the predictive  
11 value of the nomogram model with the TNM model, it was revealed that their 3-year AUC were  
12 0.758 and 0.698 ( $P < 0.05$ ) separately, and their 5-year AUC were 0.750 and 0.609 ( $P < 0.01$ ),  
13 respectively (Figure 4.).  
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## Discussion

Analysis of cases revealed that male patients accounted for more than 60% of all the elderly patients with primary liver cancer. Some statistics have presented that the mean annual change rate of men suffering from the disease is higher than that of women (3.7% vs. 2.7%) in the United States [11]. In China, a population-based study of hepatic carcinoma in Zhejiang Province demonstrated that the ASR for hepatic carcinoma was 33.24 in men compared to 1.21 in women [12]. Not only differences in lifestyle---including alcohol consumption and smoking---have led to higher cancer rates in men, but different physiological conditions such as hormone secretion and even genetic differences may be responsible for these epidemiological differences [13]. Therefore, it has been proposed that gender is a critical biological variable that should be considered in all studies aimed at improving carcinoma [14]. Analysis of baseline data also suggested that the population of elderly patients with primary liver cancer was predominantly white and mostly with the primary site in the liver, HCC histological type, grade II (moderately differentiated), T1 and without lymph node metastasis or distant metastasis. Moreover, in this population, more than half of the cases were not treated surgically. The possible reason for this phenomenon is that most of the patients were over 60 years old at the time of diagnosis, missing the best time to receive radical surgery. In addition,

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4 in consideration of the decline in their physical function as well as intolerance to surgery, a palliative  
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6 treatment was chosen for most of these patients.  
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10 Based on further univariate and multivariate COX analyses, several independent risk factors  
11 affecting the prognosis of the disease were obtained, including age, race, histological type, grade,  
12 TNM stage, surgery and tumor size. Sex, though not negligible as previously mentioned, was not  
13 a main factor affecting prognosis in this population after comprehensive analysis, which is  
14 consistent with several current retrospective studies on hepatic carcinoma [15-17]. Some clinical  
15 information affecting the operation, such as metastatic cancer, can be reflected in the TNM staging.  
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17 In terms of histological types, the prognosis of CHC is obviously worse than that of the common  
18 HCC, with a lower incidence but a higher degree of malignancy [18-19]. Analysis of the age factor  
19 revealed that the higher the age group of the patient, the worse the prognosis, suggesting a linear  
20 negative correlation trend. The nomogram model also indicated that surgery was the most crucial  
21 factor influencing the prognosis of the disease. Although just a small number of patients received  
22 liver transplantation, they showed a relatively good prognosis, followed by patients with resection  
23 or lobectomy and local destruction. In contrast, patients without surgery showed a relatively poor  
24 prognosis. This factor alone reduced the 3- and 5-year predicted survival rates to less than 50%,  
25 suggesting that the invention of new methods or enhanced surgery is still urgent for improving the  
26 prognosis of elderly patients with primary liver cancer. The influence of other factors on the  
27 prognosis of the disease is basically in line with the current consensus that the worse the grade, the  
28 higher the T-stage, the occurrence of lymph node metastasis, the occurrence of distant metastasis  
29 and the larger the tumor, the worse the prognosis of the patients.  
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46 After that, the performance of the established model was evaluated by C-Index, ROC curves  
47 and calibration curves. A nomogram model is considered to have good discrimination if its C-  
48 Index and AUC exceed 0.7 [20,21]. As the two indicators of the model constructed in this study  
49 were all above 0.7 in both the training and the validation cohorts and the calibration plots scattered  
50 in accordance with the reference line, it could be concluded that the model has good discrimination  
51 and calibration and hence the capacity to predict the prognosis of the disease.  
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58 However, this study also has shortcomings. First, the cases in this study were all from the US  
59 SEER database, which is not representative for regions outside the United States and is subject to  
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4 selection bias. In addition, the case data included in this database lacked some important ancillary  
5 tests related to the diagnosis and treatment of liver cancer, such as CEA, AST and vascular  
6 invasion. More importantly, the radiotherapy and chemotherapy information contained in this  
7 database can only be obtained by signing some agreements, which can not be obtained for the time  
8 being, so we are unable to study the relationship between radiotherapy, chemotherapy, targeted  
9 therapy and the prognosis of liver cancer [22].  
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16 There are also deficiencies in our statistical conclusions. Limited by time and skills, our  
17 model did not reach an ideal state, and its AUC is only 0.75, indicating that there is still room for  
18 improvement. This affects the prediction accuracy to a certain extent and reduces the prediction  
19 credibility. In the future, we will continue to refine our nomogram model to make it achieve a  
20 more accurate degree.  
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26 In conclusion, a nomogram model with moderate prediction was developed by using the case  
27 data in the SEER database after performing univariate and multivariate COX screening, which  
28 could provide reference for future diagnosis and treatment of elderly patients with primary liver  
29 cancer.  
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39  
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41 for-profit sectors.  
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### 47 **Conflicts of interest**

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49 The authors declare there are no competing interests.  
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### 55 **Author contributions**

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57 Fangyuan Li wrote and revised the manuscript; Ting Zheng conducted most of the analysis of data;  
58 Xuewei Gu reviewed the manuscript; All authors read and approved the final manuscript.  
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### Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

Informed consent was not required from patients to obtain data from the US SEER database since cancer is publicly reportable in every state in the United States.

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## Figure Legends

### Figure 1 Constructed nomogram

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4 **Figure 2** 3- and 5-year survival ROC curves for the training and the validation cohorts. A: 3-year  
5 survival ROC curve for the training cohort. B: 5-year survival ROC curve for the training cohort.  
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7 C: 3-year survival ROC curve for the validation cohort. D: 5-year survival ROC curve for the  
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9 validation cohort.  
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12 **Figure 3** 3- and 5-year survival calibration curves for the training and the validation cohorts. A: 3-  
13 year survival calibration curve for the training cohort. B: 5-year survival calibration curve for the  
14 training cohort. C: 3-year survival calibration curve for the validation cohort. D: 5-year survival  
15 calibration curve for the validation cohort.  
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21 **Figure 4** The comparison of ROC between the nomogram model and the TNM model. (A: 3-year  
22 nomogram model, B: 5-year nomogram model)  
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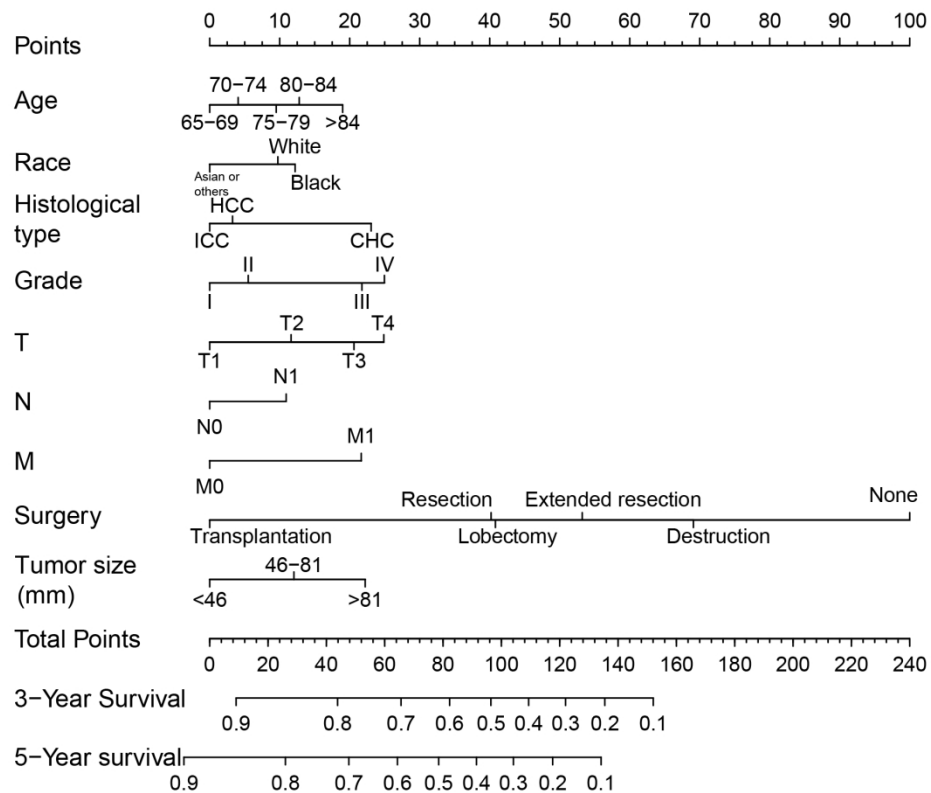


Figure 1 Constructed nomogram

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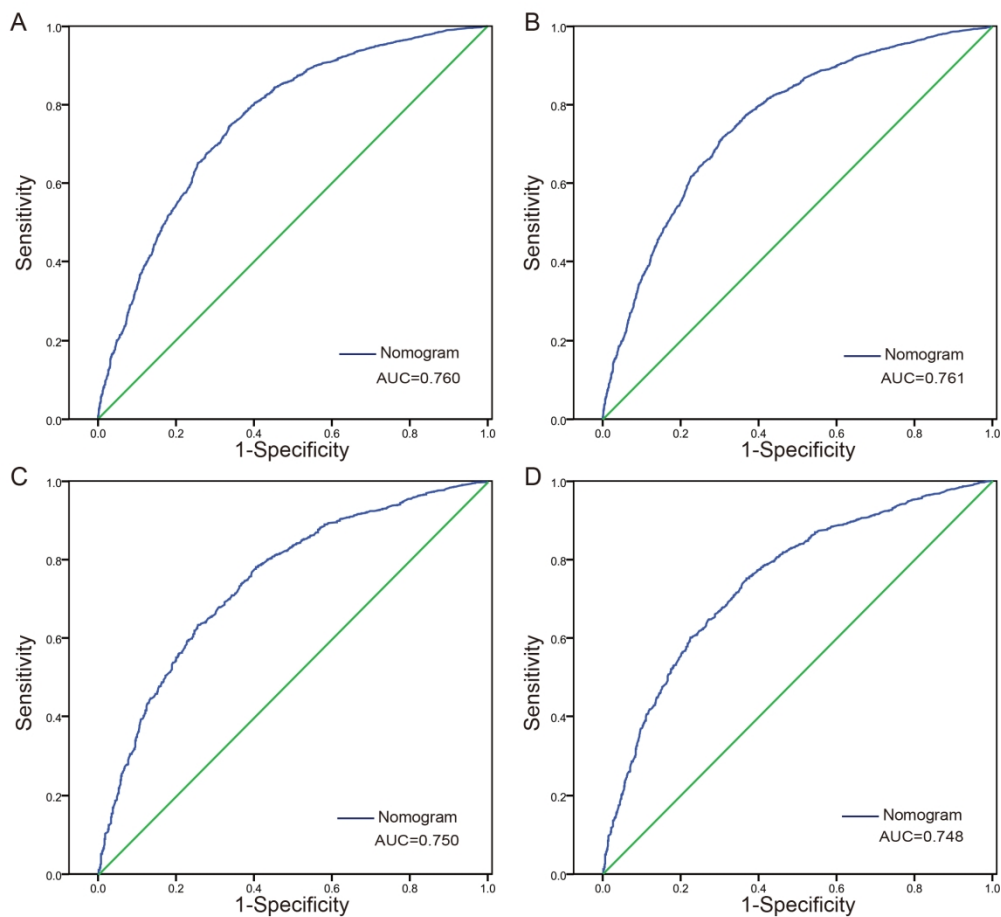


Figure 2 3- and 5-year survival ROC curves for the training and validation cohorts. A: 3-year survival ROC curve for the training cohort. B: 5-year survival ROC curve for the training cohort. C: 3-year survival ROC curve for the validation cohort. D: 5-year survival ROC curve for the validation cohort.

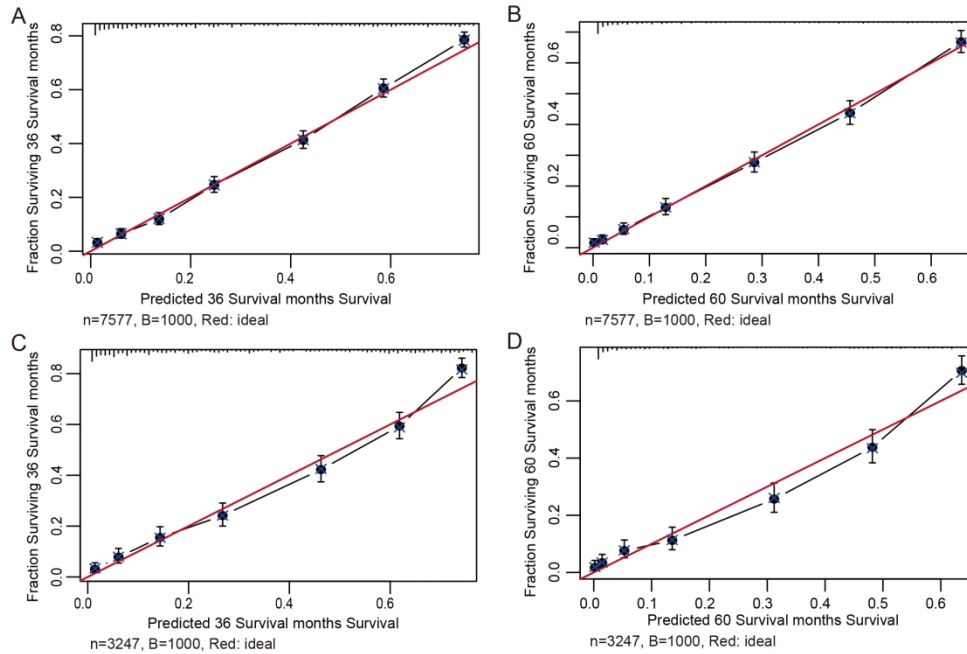


Figure 3 3- and 5-year survival calibration curves for the training and validation cohorts. A: 3-year survival calibration curve for the training cohort. B: 5-year survival calibration curve for the training cohort. C: 3-year survival calibration curve for the validation cohort. D: 5-year survival calibration curve for the validation cohort.

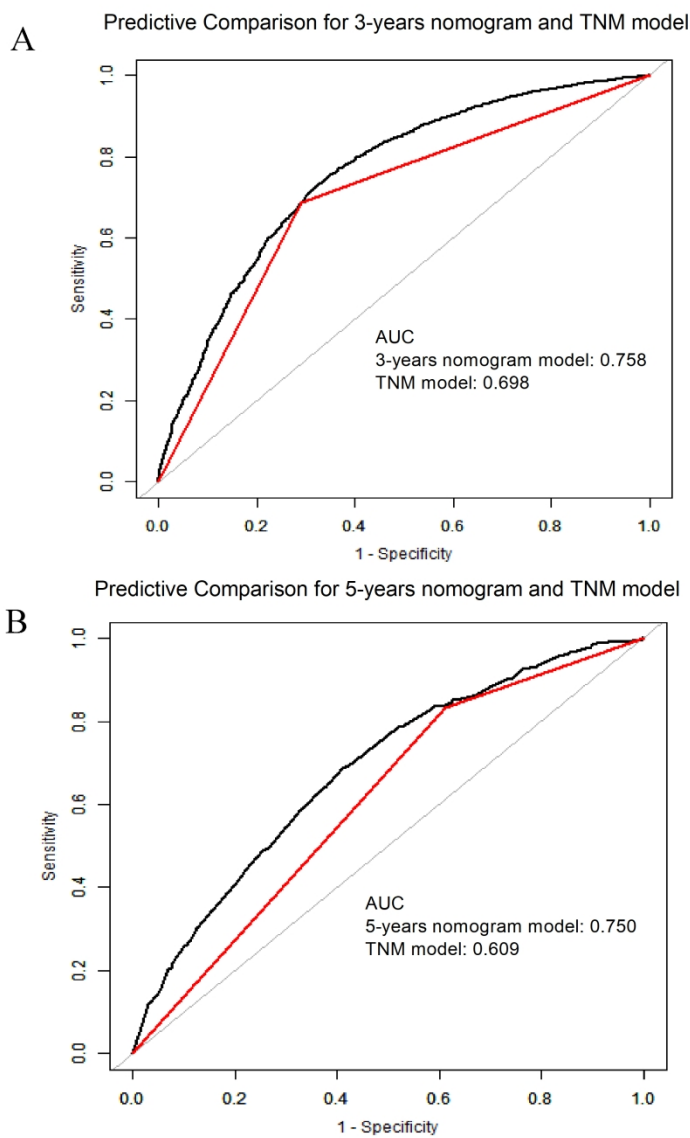


Figure.4 The comparison of ROC between nomogram model and TNM model. (A: 3-years nomogram model, B: 5-years nomogram model)

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**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology\***  
**Checklist for cohort, case-control, and cross-sectional studies (combined)**

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	5

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).